Remarks

Reconsideration of this Application is respectfully requested based on the following remarks. Claims 33-44 are pending in the application with 33 being the independent claim. Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Priority

The Examiner is of the opinion that the present application (10/816,900) is not a divisional application of Application No. 10/155,171 ("the '171 application"). Applicants respectfully disagree. Claims 81-92 of the '171 application were restricted out as directed to an independent or distinct invention in the Office Action dated December 3, 2003. Claims 33-44 of the present application directly correspond to claims 81-92 of the '171 application. Accordingly, the present application is properly named as a divisional application of the '171 application. Hence, Applicants respectfully request that the Examiner reconsider the objection to the priority claim.

Double Patenting Rejections

Claims 33-44 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 33-41 of co-pending Application No. 11/081,641 and claims 33-54 of co-pending Application No. 11/081,640. *(Office Action, page 3)*. Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [a]lthough the conflicting claims are not identical, they are not patently distinct from each other because in both cases,

> the claims are drawn to a composition and/or solution and/or kit comprising between .00018 mg and about 0.45 mg phentolamine mesylate or a molar equivalent of another alpha adrenergic receptor antagonist and a pharmaceutically acceptable carrier present in container that fits into a standard dental local anesthetic syringe.

(Office Action, page 3).

Applicants respectfully disagree. Applicants have *concurrently* filed a terminal disclaimer over co-pending Application No. 11/081,641 and co-pending Application No. 11/081,640 with this response. Therefore, the rejection has been rendered moot. Accordingly, Applicants respectfully request that the rejection under obviousness-type double patenting be withdrawn.

Claims 33-44 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-12 of U.S. Patent No. 6,872,390. *(Office Action, page 3).* Applicants respectfully traverse this rejection.

The Examiner stated that:

> [a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because in both cases, the claims are drawn to a composition and/or solution comprising between .00018 mg and about 0.45 mg phentolamine mesylate or a molar equivalent of another alpha adrenergic receptor antagonist and a pharmaceutically acceptable carrier present in container that fits into a standard dental local anesthetic syringe. Further, the instantly claimed invention encompasses the claimed invention of 6,872,390.

(Office Action, page 3-4).

Applicants respectfully disagree. Applicants have *concurrently* filed a terminal disclaimer over U.S. Patent No. 6,872,390 with this response. Therefore, the rejection

has been rendered moot. Accordingly, Applicants respectfully request that the rejection under obviousness-type double patenting be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 33-35, 38, 39 and 40 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Booth *et al.* (U.S. Pat. No. 4,508,715). *(Office Action, page 4)*. Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> Booth et al. anticipate the claimed invention (see e.g. example IV and example IX, column 9 lines 56-59, example XII and XIV) because Booth teaches a composition comprising a molar equivalent of an alpha adrenergic receptor antagonist (i.e. 0.125 mg of yohimbine in a syringe for injection to a subject) and a pharmaceutically acceptable carrier. Therefore, the reference is deemed to anticipate the claimed invention.

(Office Action, page 4).

Applicants respectfully disagree. In order to anticipate and render pending claims unpatentable under § 102(b), the Booth *et al.* reference must teach all elements of the claimed invention. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (holding "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference").

In the present case, Applicants claim:

> [a] unit dose of a composition, said unit dose comprising between about 0.0018 mg and about 0.45 mg phentolamine mesylate or a molar equivalent of another alpha adrenergic receptor antagonist and a pharmaceutically acceptable carrier for administration to a mammal.

The dosage of about 0.0018 mg to about 0.45 mg phentolamine mesylate is equivalent to about 4.78×10^{-9} moles[1] to about 1.19×10^{-6} moles, respectively. Booth *et al.* do not inherently or expressly teach all the elements of Applicants' invention. Namely, Booth *et al.* do not teach the dosage element of the claimed invention. For instance in Example IV Booth *et al.* injected 0.125 mg/kg yohimbine hydrochloride ("yohimbine") into a 14 kg dog to reverse the effects of previously administered anesthesia. This corresponds to a dosage of 1.75 mg yohimbine[2], which is equivalent to 4.47×10^{-6} moles. A dosage of 1.75 mg yohimbine does not fall in the claimed range of about 0.0018 mg to about 0.45 mg or a molar equivalent thereof.

Furthermore, in Example IX, Booth *et al.* injected 0.125 mg/kg yohimbine into steers weighing 227 - 290 kg to reverse the effects of previously administered anesthesia. This corresponds to dosages of 28.37 mg - 36.25 mg yohimbine which is equivalent to 7.25×10^{-5} moles to 9.27×10^{-5} moles, respectively. Dosages of 28.37 mg - 36.25 mg do not fall within the claimed range of about 0.0018 mg to about 0.45 mg or a molar equivalent thereof. Moreover, in Example X, Booth *et al.* injected 0.125 mg/kg yohimbine into dogs weighing 10 - 20 kg to reverse the effects of previously administered anesthesia. The preceding corresponds to 1.25 - 2.50 mg yohimbine, which

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[1] *Conversion of milligrams (mg) to moles:* The dosage (mg) was converted to moles by (1) dividing the dosage (mg) by 1000 to obtain dosage (g) and (2) dividing dosage (g) by the molar mass of phentolamine mesylate ($gmol^{-1}$). The molar mass for phentolamine mesylate is 377.459 $gmol^{-1}$.

[2] *Conversion of dosage (mg/kg body weight):* The dosage of yohimibine was converted to milligrams (mg) by multiplying the weight of the subject (in kilograms) with the dosage (0.125 mg/kg body weight). Then the dosage (mg) was converted to moles by (1) dividing dosage (mg) by 1000 to obtain dosage (g) and (2) dividing dosage (g) by the molar mass of yohimbine hydrochloride ($gmol^{-1}$). The molar mass for yohimbine hydrochloride is 390.903 $gmol^{-1}$.

is equivalent to 3.19×10^{-6} moles to 6.39×10^{-6} respectively. Yet again, dosages of 1.25 - 2.50 mg do not fall with the claimed range of about 0.0018 mg to about 0.45 mg or a molar equivalent thereof.

In addition, in Examples VIII and XIV, Booth *et al.* injected 0.125 mg/kg yohimbine into dogs. As demonstrated Examples IV and X, the weight of the dogs necessitates a dosage of yohimbine to reverse the effects of previously administered anesthesia that does not fall within the claimed range of about 0.0018 mg to about 0.45 mg or a molar equivalent thereof. The same is true in Example XII where Booth *et al.* used a horse as a subject. Based on the weight of the horse the dosage of yohimbine needed to reverse the effects of previously administered anesthesia does not fall within the claimed range of about 0.0018 mg to about 0.45 mg or a molar equivalent thereof.

Indeed, no example in Booth *et al.* utilizes a dose of less than 0.125 mg/kg yohimbine per body weight to reverse the effects of previously administered anesthesia. Furthermore, Booth *et al.* teaches in general that 0.125 mg/kg body weight is the dose of yohimbine that effectively reverses the effects of previously administered anesthesia. *(See, column 5, lines 27-31; column 11, lines 11-13).*

Based on the foregoing, Booth *et al.* do not teach the dosage element of the claimed invention. Namely, Booth *et al.* do not teach the claimed unit dosage of a composition of phentolamine mesylate or another adrenergic receptor antagonist. In fact, the dosages disclosed in Booth *et al.* are substantially greater than the range of the claimed invention. Accordingly, Booth *et al.* do not anticipate the claimed invention. Therefore, Applicants respectfully request that the preceding rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 33-40 and 42-43 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Booth *et al.* (U.S. Pat. No. 4,508,715). *(Office Action, page 5).*

Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> Booth et al. do not expressly teach the composition is a solution formulated for topical application and the unit dosage of the solution present in a container that fits into a standard dental local anesthetic syringe. However, based upon the overall beneficial teachings provided by Booth et al., the result-effective adjustment of conventional working conditions therein (e.g. the substitution of one type of administration for another such as the solution used topically instead of by injection and the form of the solution being placed in the container first than into a syringe), is deemed merely a matter of judicious selection and routine optimization which is well with the purview of the skilled artisan.
>
> Accordingly, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

(Office Action, page 5-6).

Applicants respectfully disagree. Pursuant to M.P.E.P. § 2143, three criteria must be met to establish a *prima facie* case of obviousness: (1) there must be a suggestion or motivation to a person of ordinary skill in the art to modify the reference, (2) there must be a reasonable expectation of success, and (3) the reference must teach or suggest all the claim limitations.

In the present case, none of the three preceding criteria has been satisfied. First, Booth *et al.* do not suggest or provide motivation for a person of ordinary skill in the art to modify the reference to arrive at the presently claimed invention. In fact, Booth *et al.* teach dosages of yohimbine that are far greater than the claimed unit dose compositions.

Moreover, throughout the patent Booth *et al.* teach the use of yohimbine at a dose of 0.125 kg/mg body weight to reverse anesthesia in animals. For instance, in Examples IV, IX and X, Booth *et al.* teach yohimbine dosages of 1.75 mg, 28.37 - 36.25 mg and 1.25 - 2.50 mg for 14 kg dogs, 227-270 kg steers and 10 - 20 kg dogs respectively. The dosages disclosed in Booth *et al.* are substantially greater that the claimed dosage range of about 0.0018 mg to about 0.45 mg. For example, the 36.25 mg dosage used in the 227 kg steer is approximately 78- to 20,000- fold greater than the presently claimed dosages. Further, Booth *et al.* do not provide any suggestion or motivation to use lower dosages of yohimbine. *See In re Wiggens*, 397 F.2d 356, 360 (C.C.P.A. 1968)(holding that a claimed invention was not obvious over the prior art reference teaching the same compound in an amount less than the claimed invention when there was no suggestion in the reference to prepare or administer composition in the greater amounts of the compound). Thus, one of ordinary skill in the art would not be motivated to lower the dosages of yohimbine to the molar equivalent of about 0.0018 mg to about 0.45 mg.

Second, the disclosures in Booth *et al.* do not provide a reasonable expectation that the dosages of about 0.0018 mg to about 0.45 mg of the claimed invention would be successful in effectively reversing the effects of previously administered anesthesia. In fact, Booth *et al.* do not teach or suggest doses below 0.125 mg/kg of yohimbine and instead direct one to doses of 0.125 mg/kg and above. *(Column 11, lines 11-13).* A dose of 0.125 kg/mg is equal to 9.37 mg for a 75 kg person. Thus, a person of ordinary skill in the art would not reasonably expect that lower doses would be successful in reversing anesthetic effects. Accordingly, based on the disclosures in Booth *et al.* a person of

ordinary skill in the art would not reasonably expect that lower doses would have any effect on the reversal of the anesthetic effects.

Since there is no motivation to modify the teachings of Booth *et al.* to arrive at the claimed dosages and no reasonable expectation of success if lower doses of phentolamine mesylate or another α-adrenergic receptor antagonist are used, the Examiner has not established a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the foregoing rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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